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Hot saline irrigation as an alternative local adjuvant therapy in local aggressive bone tumors

Lokal agresif kemik tümörlerinde alternatif bir adjuvan tedavi olarak sıcak su uygulaması

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Amaç: Lokal agresif tümörlerde küretaj sonrası kavite duvarında kalan mikroskobik kontaminasyonun biyolojik inaktivasyonu için alternatif bir termoinaktivasyon yöntemi geliştirmek amacıyla, turnikeli ve turnikesiz ortamda kemik kavitelerine uygulanan değişik sıcaklıklardaki suyun, kavite duvarındaki kemik bölgesinde oluşturduğu sıcaklıklar ve etkileri *in vivo* olarak araştırıldı.

Çalışma planı: Dokuz adet dişi erişkin koyunun turnikeli veya turnikesiz arka bacaklarında, kondiler bölgelerde 12 cm^3 hacminde açılan kavitelere her biri 12 dakika süreyle aralıklı 60, 70, 75, 80 veya 100 °C sıcaklıkta serum fizyolojik uygulandı. Isının kavite duvarına 1, 2, 3 ve 10 mm uzaklıklarda yarattığı sıcaklıklar kaydedildi. Deneklerin yaşamı işlem sonrası 2. gün, 3 ve 6. haftalarda ve 3 ve 7. aylarda sonlandırılarak histolojik olarak incelendi.

Sonuçlar: Ameliyat öncesinde deneklerin vücut ısısı ortalama 38.1 °C, kemik içi ısısı ortalama 27.4 °C ölçüldü. Turnike uygulaması, kemikte ortalama 1.5 °C (dağılım 1-2 °C) sıcaklık azalmasına neden oldu. Seksen derecenin altındaki ve 80 °C'deki uygulamalarda kemik kavitesi içinde ölçülen en yüksek sıcaklıklar sırasıyla 55.5 °C ve 62.5 °C, kemikte ölçülen en yüksek sıcaklıklar 40.5 °C ve 42.5 °C idi. Sıcaklık 100 °C'ye çıkarıldığında yumuşak doku, kas dokusu ve kemikte yeşil-kahverengi-siyah renk değişikliği görüldü ve denek ameliyat sonrası ikinci günde kaybedildi. Diğer sıcaklıklarda çevre kemik, kas, yumuşak dokular normal renkteydi ve bu deneklerde ameliyat sonrası erken komplikasyon gelişmedi. Histolojik incelemede, 60 °C uygulamalarında kavitede kemik iliği ve kemikte nekroz görülmezken, 70 ve 75 °C'de kemik iliği nekrozu görüldü; 80 °C'de ise kemik iliği nekrozuna ek olarak, kemik nekrozu izlendi. Bu sıcaklıklarda deneklerin hiçbirinde yumuşak doku nekrozu görülmedi.

Çıkarımlar: Bulgularımız, kemik kavitelerindeki sıcak serum fizyolojik uygulamalarında, kavite duvarındaki 1-2 mm'lik kemik bölgesinde kemik nekrozu oluşturabilecek en uygun sıcaklığın 80 °C olduğunu göstermektedir.

Anahtar sözcükler: Kemik neoplazileri/tedavi; femur/cerrahi; ısı; hipertermi oluşturma/yöntem; nekroz; koyun; su/terapötik kullanım.

Objectives: This study aimed to develop an alternative thermoinactivation method for biological inactivation of microscopic contamination on the cavity wall following curettage of local aggressive tumors. Hot saline irrigation was applied at various temperatures to bone cavity, with or without tourniquet on the extremity and temperature changes and local effects were investigated *in vivo*.

Methods: Bone cavities 12 cm^3 in size were created in the condylar regions of the hind legs in nine female adult sheep. The cavities were irrigated by hot saline solution at 60, 70, 75, 80, or 100 °C, with and without the presence of a tourniquet, and the temperatures 1, 2, 3, and 10 mm distant to the cavity wall were recorded. The animals were sacrificed postoperatively at 2 days, 3 and 6 weeks, and 3 and 7 months for histologic studies.

Results: The mean body temperature and temperature inside the bone prior to surgery were measured as 38.1 °C and 27.34 °C, respectively. Tourniquet application caused a mean decrease of 1.5 °C (range 1-2 °C) in bone temperature. The highest temperatures measured below 80 °C and at 80 °C were 55.5 °C and 62.5 °C in the cavity, and 40.5 °C and 42.5 °C in the bone, respectively. At 100 °C application, the color of the bone together with the surrounding soft tissue and muscle tissue turned to yellow-brown-black, and the animal died on the second postoperative day. At temperatures ≤80 °C, the color of the bone and surrounding tissues appeared normal and no early complications were encountered. Histologic studies showed no bone marrow or bone necrosis at 60 °C, only bone marrow necrosis at 70 °C and 75 °C, and in addition to bone marrow necrosis, bone necrosis at 80 °C. At these temperatures no evidence for soft tissue necrosis were observed.

Conclusion: Our results show that, in order to achieve bone necrosis at 1-mm and 2-mm distances from the cavity wall, the optimum temperature for hot saline irrigations applied to the bone cavity is 80 °C.

Key words: Bone neoplasms/therapy; femur/surgery; heat; hyperthermia, induced/methods; necrosis; sheep; water/therapeutic use.

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In local aggressive tumors (such as chondroblastoma, chondromyxofibroma, osteoblastoma, desmoplastic fibroma, benign fibrous histiocytoma, aneurysmal bone cyst, giant cell bone tumor, chordoma, enchondroma, low grade chondrosarcoma, schwannoma), local adjuvants (high speed burr, liquid nitrogen or cryosurgery with argon helium, hydrogen peroxide, phenol, ethanol, etc.) are frequently added to the curettage procedure to render the microscopic tumor contamination remaining on the walls of the tumor cavity biologically inactive.[1,2,3,4,5,6,7,8,9,10] Numerous studies in the literature discuss the use of hyperthermia in tumor activation, however hyperthermia in clinical settings is often a result of the heat generated by burrs and the curring of cement. In this type of treatment however, the distribution and conduction of heat as well as its biological effects with respect to the distance from the area of heat application in tissues with normal versus temporarily ceased blood flow (tourniquet) are not known.

Assuming that the heat generated will be able to penetrate the 200-300 micron-thick cavity wall remaining from the curettage of the local aggressive tumors, this study aims to determine the optimum heat which will achieve tissue necrosis at a depth of 2 mm, and also to determine the time needed to preserve the heat with and without the application of a tourniquet. Although this method is a simple, cheap and clinically applicable thermoactivation technique widely used in the surgical treatment of local aggressive tumors, information is limited. In particular, there is no information regarding the temperature of the hot saline solution that will be applied.

Hot saline technique was first applied by our team, and constituted the pilot study of a device that we are developing. In a previous, we showed that when hot water at 70 °C was applied to a 20 cm3 bone cavity, it heated the cavity wall more compared to cement. We therefore think that hot water will be a more effective local adjuvant than cement in the inactivation of tumor contamination that remains on the cavity wall.

Materials and method

The study is approved by the ethical committee. 10 female sheep from Ovis aries strain Dağlıç breed were included in the study. Mean weight of the animals was 33.73 (30.6-36)kilograms. Distal epiphyseal plates in sheep close approximately after age 3, therefore animals older than 4 years were selected for the study. In all animals, body temperature was measured prior to the procedure, and was found to have an average value of 38.13 (37.6-38.7) °C. Bilateral anteroposterior and lateral direct x-rays of the knees on posterior legs were obtained. One back leg of each sheep was operated. A 12 cm3 cavity was created in the distal femur. Hot saline at 60, 70,75 , 80 and 100 °C were applied to cavities with and without the presence of tourniquet. Temperature changes in the cavities, bone areas 1,2, 3mm and 1 cm distal to the cavity wall, and also in the joint adjacent to bone were recorded. The histologic and radiologic changes were evaluated.

Surgical technique

The animals were operated in the operation rooms of Istanbul University Veterinary Faculty Surgical Sciences Department. The procedure was carried out on one hind leg. Mean operation room temperature was measured as 21.45 (18.4-24) °C. The operative sites were shaved with razor before the operation. General anesthesia induction was made with intramuscular injection of 2mg Rompun (Xylazine hydrochloride, 50 cc vial 2%, 1cc 23, 32 mg active substance, produced by Mefar Pharmaceuticals, license by Bayer, Turkey) at time 0. Peripheral line was inserted, and 5 mg Ketalar (Ketamine hydrochloride 10ml, 50mg/ml, Parke Davis Eczacıbaşı, Turkey) was given on the 15th minute. The animals were intubated with 8.0 or 8.5 intubation tube, and the cuffs were inflated. Inhalation anesthesia was made with Isoflorane 75 ml (Forane100 ml, Ohio, Abbott Pharmaceuticals, Turkey), initiated at 4% MAC (Minimal Alveolar Concentration) and maintained at 2.5% MAC with a semi-open anesthesia method.

The right ear of each animal was marked with a bovie, from 1 to 10. All animals received prophylactic Cephazoline (Sefazol 1g, İbrahim Ethem Pharmaceutical Company, Turkey). Anesthesia duration was 2 hours. The animals were then positioned into lateral decubitus position. Skin was prepped with Betadine soap solution (7.5% povidone soap, Kansuk Pharmaceuticals, Turkey), then washed with Betadine antiseptic solution (10% polyvinylpolidone iodine, Kansuk pharmaceuticals, Turkey). After sterile draping, the operative site was cleaned with 70% alcohol solution. In the tourniquet

group, blood flow was ceased with Esmarch bandages wrapped on the superior aspect of the femur.

A 1 cm long incision was made 1 cm above the lateral aspect of the knee joint. Layers of the skin and fascia were cut. A 1 cm deep hole was created on the lateral femoral condyle and the A1 probe was inserted into this hole. Temperature inside the bone was measured to be 27, 37 (25, 5-29, 6) °C. A1 probe was removed and the incision was extended proximally on the femur and completed to 4 cm The skin and fascial layers were opened, access to the lateral condyle was gained between the lateral vastus and biceps muscles. The periosteum was stripped. A total of 4 holes, 2 superiorly and 2 inferiorly, were opened with 1 cm in between the holes. The holes were joined and elliptical piece of cortex was removed from the bone. The femur was curetted from the metaphysis to the subchondral bone over the lateral condyle. Curettage continued until a bone volume of 12 cm^3 was reached. The volume of the cavity was verified by filling with sterile saline. After the desired volume was reached, 4 holes were created, each 1 cm deep and 1, 2, 3 mm and 1 cm away from the cavity wall.

A1, A2, A3 and A4 probes were inserted to the holes opened 1,2,3 mm and 1 cm from the cavity wall, respectively. Probe A5 was inserted into the joint by penetration of the joint capsule, and A6 was inserted into the bone cavity. Temperature changes in the bone and the joint were recorded with ABB PR 106 device. Experimental setup is demonstrated in Figure 1.

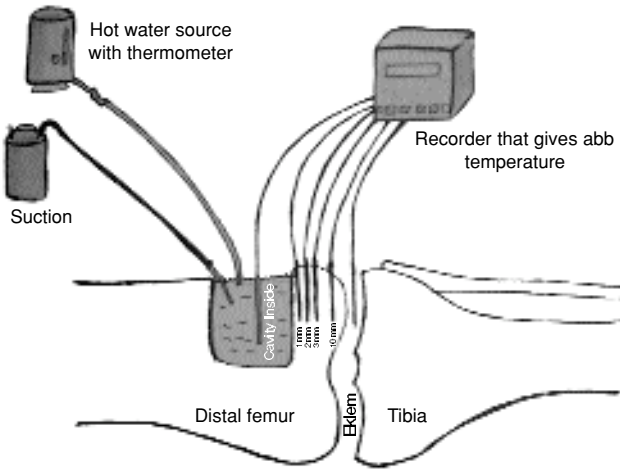

Figure 1. Experimental set up scheme

The cavity was filled with 12 cm^3 hot saline at 60, 70, 75, 80, 100 °C which was applied intermittently and kept within the cavity for 1 minute in each application. After each application the fluid was aspirated, and irrigation continued for 12 minutes. Temperature changes were recorded until the measurements dropped below body temperature. Any fluid remaining in the cavity was aspirated after the recordings were completed. The periosteum, fascia and skin were closed in layers. The animals were extubated 3-4 minutes after cessation of forane inhalation. AP and lateral X rays of the knee were obtained and the animals were taken to the recovery room, and later housed with the other animals next day. In the postoperative period, all animals received intramuscular injections of 1 g cephazoline (Sefazol 1 gr vial) and 80 mg gentamycin sulphate (Genta 80 ampule, İ.E.Ulagay) every 12 hours, for a total of 4 days.

Radiologic follow up was carried out at different intervals and the animals were sacrificed at different periods (postoperative second day, third week, third and seventh months), and histologic samples were obtained. The samples were preserved in 10% buffered formaline solution overnight. The next day, bone samples were split and photographed longitudinally. Samples from the cavity wall were softened in formic acid, and embedded into paraffin blocks after routine tissue processing methods. 4 micron thick samples were taken, stained with hematoxylin and eosin, and examined under the light microscope.

Quantitative comparison of the animals with and without tourniquet was made with Mann-Whitney U test (p values below 0.005 were considered statistically significant). Correlation between the temperature of the saline and distance were determined with Pearson correlation. Relationship of temperature values at each distance was measured with curve

Table 1. Study design

Temperature of saline Solution	Number of Sheep	Survival time after the test
60 °C	2	3 and 6. weeks
70 °C	2	6 weeks and 7 months
75 °C	2	3 and 6. weeks
80 °C	2	6 weeks and 7 months
100 °C	1	Death on the 2nd day

Table 2. Highest temperature values obtained with hot saline at 60, 70, 75, 80 ve 100 °C with and with out tourniquet.

	Without tourniquet					With tourniquet			
	60 °C	70 °C	75 °C	80 °C	100 °C	60 °C	70 °C	75 °C	80 °C
1 mm	39.0	35.0	40.0	42.5	44.5	36.0	40.5	40.0	42.5
2 mm	35.0	34.0	38.0	39.0	43.0	35.5	39.5	37.0	39.5
3 mm	36.0	34.0	37.0	33.0	41.0	33.0	34.0	35.0	33.7
1 cm	32.5	32.0	33.0	31.0	33.0	33.0	35.0	37.0	31.8
Adjacent joint	30.0	38.0	34.5	31.0	35.0	30.0	30.0	31.0	31.5
Cavity centre	53.0	54.0	53.5	62.5	66.0	52.0	52.0	55.5	62.0

estimation test. Correlation between tourniquet usage and temperature were measured with Spermann correlation.

A.B.B. PR 106 RECORDING DEVICE: This is a 6 channel multipurpose measurement and recording device that can measure and record temperature changes between 0-100°C, both graphically and digitally. The device has a 6 channel microprocessor with thermocouple input. Milliampere, millivolt and ohm inputs can be adjusted on the device. It has a two line LCD display with backlight. Recording speed is 1-1500 mm/sec, accuracy rate ± 0.1%. Possessing a totalizer that has the capability to add an analog output with seperate on-off control for every channel, the device has programmable 85-265 VAC 50/60 Hz feedback tension, and measures 144x144x230 mm. (ABB-PR-106 Kent Taylor Co. United Kingdom)

Results

The temperature, radiographic, and histologic findings were analysed in the group which underwent application of hot saline at 60, 70, 75, 80,100 °C into the 12 cm^3 cavity with and without the presence of tourniquet.

In the animal which had a mean body temperature 38.18 °C (38 – 38,3 °C), average temperature inside the bone was measured as 27,37 °C (27,1 – 27,42 °C). The temperature inside the bone dropped by 1.5 °C (1-2) after the application of the tourniquet.

In hot saline application groups with and without tourniquet, the highest temperatures measured in six points; 1,2,3 and 10 mm away from the cavity, neighboring the joint and inside the joint are shown in Table 1 below. In applications where saline was under 80°C, the highest temperatures measured in the bone cavity and bone were 55.5°C and 40.5°C, respectively. These results were 62.5°C and 42.5°C, again respectively, where the saline was at 80°C. In the animal where the saline was at 100 °C and applied without tourniquet, the application field showed a green-brown-black discoloration in the soft tissue, muscle and bone. This animal died on the second postoperative day. Autopsy revealed widespread necrosis in the neighbouring soft tissues, muscle and bone. Therefore, 100°C saline application was cancelled. In the animals which received saline at 80°C, the soft tissues, muscle and bone had a normal color, these animals did not develop any postoperative complications. None of the saline applications formed a temperature gradient that would destroy the joint.

The knee region of each animal was examined macroscopically and microscopically in Istanbul University Cerrahpasa Medical Faculty Pathology Department. After the animals were sacrificed, muscles over the distal femur were stripped and the femur was bisected longitudinally in the intercondylar region.

Macroscopic examination of the cavity showed that in the first week there was a tissue defect with fresh bleeding and slightly irregular borders. On the third week, there was a yellow green fibronecrotic tissue, and on the third month, there was a white shiny fibrotic tissue. It was seen that the cavity was gradually filled as the granulation tissue turned into scar tissue with the aid of fibroblastic activity.

There was no necrosis in the animals where the saline was at 60°C. There was bone marrow necrosis in the 70°C and 75°C groups (Figure 2), and in the 80°C group, as well as cellular osteon loss and bone necrosis with destruction of regular lamellar structure in addition to bone marrow necrosis (Figure 3). None

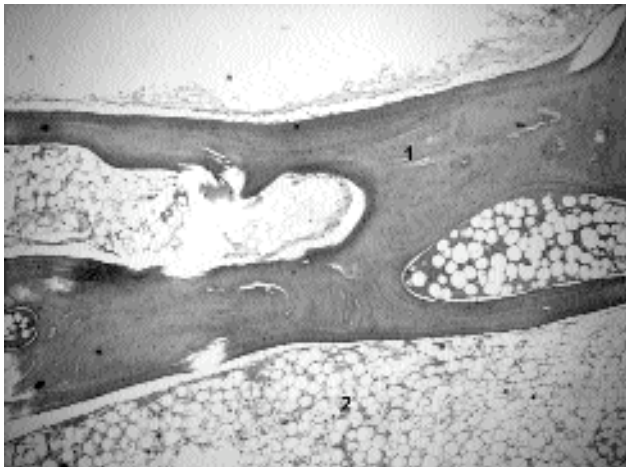

Figure 2. Tissue section obtained from group that underwent application with saline at 70°C. Tissue sample is obtained at the 7. month and shows only bone marrow necrosis. 1: Osteocytes within trabecular structure. 2: bone marrow necrosis and weak osteoblastic activity .

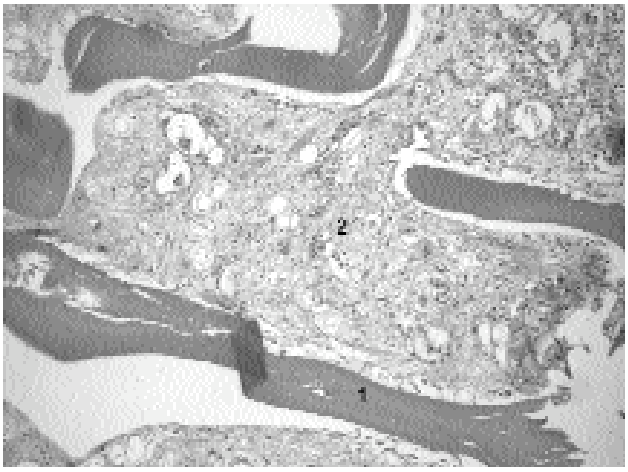

Figure 3. Tissue section from an animal that underwent application with saline at 80°C and sacrificed on the 3rd week. 1: Trabecular structure and osteons are disrupted. Empty osteocyte lacunes show bony necrosis. 2: Fat necrosis is present in bone marrow, and there is hardly any osteoblastic activity. These point to irreversible bone necrosis.

of the animals showed soft tissue necrosis. Fatty degeneration showing bone marrow necrosis in 70°C and 75°C hot saline application. Presence of live osteoblasts in osteocyte lacunes shows that the necrosis is limited to the marrow space.

Pearson correlation analysis showed a good correlation between the water temperature and the temperature detected at 1 mm (r =0.793) and 2 mm (r =0.856), and a significant correlation between the (r =0.878) inside the cavity. There was a good correlation between the temperature detected in the cavity and the temperatures detected at 1 mm (r=0.795) and 2 mm (r=0.743)

Curve estimation tests showed that temperature values at 1mm and 2 mm increased linearly, while at 3

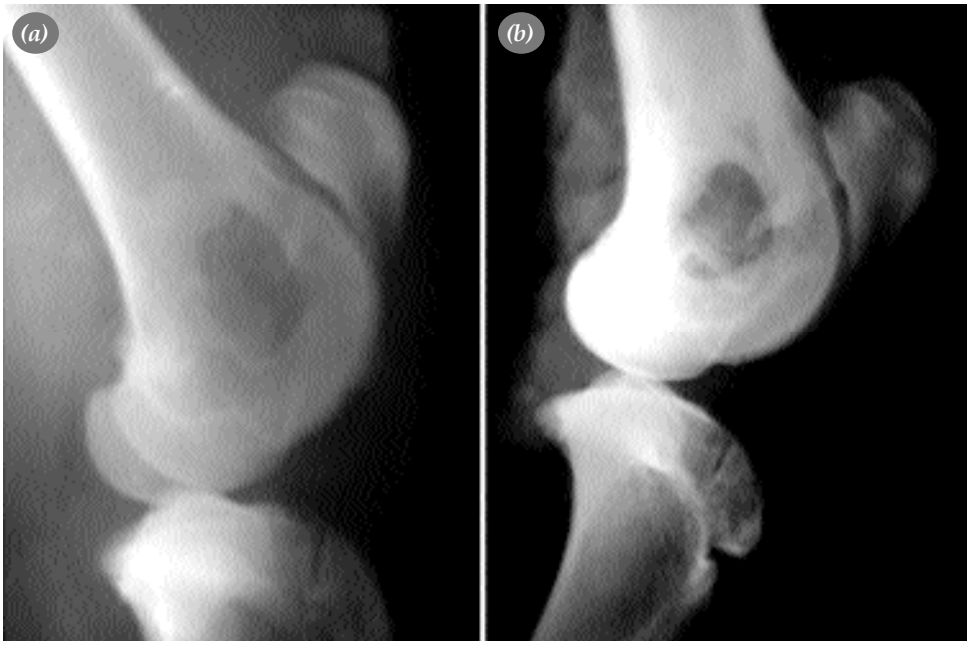

Figure 4. (a) X ray on postoperative day 1; **(b)** on postoperative 3rd month.

mm there was a cubic relationship. At 80°C application, temperatures showed a sudden increase in the probes 3mm away. There is also a linear relationship in the joint and cavity. There was no relationship between the values obtained at 1 cm. In the animals with and without tourniquet, there was no significant difference in the temperature values according to Mann-Whitney U test. According to Spermann correlation, the decrease that occurs after tourniquet release are correlated. There was a moderate correlation (r =-0.437), at 3 mm, the point where the greatest drop in temperature was observed.

Radiologic investigations show that initially all cavities have irregular borders, which in time become more clear, circular and smaller. (Figure 4a-b)

In conclusion, hot saline at 80°C applied for 12 minutes created a maximum temperature of 42.5°C in the bone as well as 1 and 2 mm locations, and was determined as the optimal temperature that created irreversible bone and marrow necrosis. None of the saline applications resulted in a heat gradient that would injure the joint.

Discussion

This study showed in vivo that bone tissue possessed lower temperatures compared to soft tissues. Thermal conductivity (k) of bone is 0.0009 cal/sec/cm^2/ C/cm, density(p) 2.6 g/cc, specific heat 0.162 cal/g/C. Thermal conductivity (k) of cement is 0.0004 cal/sec/cm^2/ C/cm, density (p) 1.19 g/cc, and specific heat 0.35 cal/g/C. Thermal conductivity (k) of water is 0.0015 cal/sec/cm^2/ C/cm, density (p) 1 g/cc, and specific heat 1 cal/g/C. 0.0015 cal/sec/cm^2/ C/cm. When bone,saline and cement are compared, bone has the lowest coefficient for thermal conduction, highest density and lowest specific heat. As a result, bone is a poor conductor of heat, with less vascularity and lower specific heat compared to soft tissues.[12,13] Therefore, bone temperature is lower than soft tissues. There was a 1.5°C (1-2)drop in temperature within the bone after the aplication tourniquet, which can be explained by decreased perfusion.

Numerous methods have been proposed to inactivate the microscopic tumor contamination remaining on the cavity walls.[1,2,3,4,5,6,7,8,9,10] Normal human cell begins to lose function when local temperature exceeds 41 °C. On the other hand, in tumor tissue, blood flow increases at 41 °C, initially increases and then decreases at 43 °C, and decreases significantly at 45°C.[14] In agreement with the study of Akagi et al., we observed radiologically and histologically that antitumoral effects of heat in bone tissue started at temperatures above 42.5°C.[15] It is noteworthy that although normal human cells die at 41°C, tumor cells die at temperatures above 42.5°C.[16] The epiphysis and cartilage are the most resistant parts of bone against heat. Viable cells are observed in epiphyseal tissue heated to 55°C. Bone heated to and above 50°C failed to show any cell development in cultures. Temperatures above 70°C are reported to decrease bone strength, and temperatures above 90°C significantly decrease the load needed to fracture bone and to separate bone edges.[17]

In their experimental study,[18] Berman et al. designed a fluid probe that would deliver hot saline at fixed temperatures onto deperiosted bone in the proximal tibia of rabbits. Saline temperatures ranged from 45 °C and 90 °C for a standart exposure time of one minute. Bone tissue biopsies were taken in the 1.,2. and 3. postoperative weeks and thermal injury limits and regeneration potentials were investigated. Control group was also included to observe the reaction of bone to the surgical procedure. Bone necrosis was constantly seen in temperatures beginning from 70°C and macroscopically presented as a brown-blue-black discoloration. Histologic sections showed bone necrosis in all subjects subjected to scald temperatures above 70°C. In temperatures above 70°C neighboring tissues displayed coagulation necrosis at various degrees which could not be prevented with copious irrigation with cold water. This necrosis however, did not result in a delay or a problem in wound healing. In control animals and animals subjected to saline at 45-55 °C, there was early inflammatory reaction due to surgery and subsequent fibrous tissue scar, and no bone or bone marrow necrosis. At temperatures below 70°C there was no cortical bone necrosis, but different levels of bone marrow necrosis were seen. Histologic findings of thermal bone necrosis were first seen at 70°C, consisting of cellular osteon loss and disruption in regular lamellar structure. In temperatures above 70°C, bone necrosis was seen at increasingly deeper levels, and at 85°C, cortical bone showed a full thickness necrosis, which was 1.5mm thick at

the application site. The results of the study on the other hand, were reported to be inadequate to evaluate bone regeneration after bone necrosis.[18]

There are many factors that affect the conduction of heat, e.g. local temperature, heat conduction coefficients of the substances through which heat will be dissipated, contact area between two substances, and heat losses due to miscallenous reasons. Compared to other other tissues in the body, bone has a lower coefficient of heat conduction. Therefore, even in conditions where the saline temperature is 100°C, the temperature of fluid inside the bone cavity and of the surrounding bone does not exceed 66°C and 44.5°C, respectively. Even at these levels, the heat resulted in green-black discoloration in bone and nieghboring tissues, a sign of diffuse necrosis, eventually leading to death of the animal on the second postoperative day. Autopsy of the leg and microscopic studies revealed diffuse necrosis in bone, muscle and other soft tissues. The heat has antitumoral effects in bone tumors and the heat generated by the curring of cement and the burr is considered to serve such a purpose. However, studies have shown that large masses of cement is required for the curring reaction to generate enough heat for bone necrosis.[11, 14] Necrosis caused by cement is not a result of the heat per se, but rather the toxic effect of the monomer released during curring and the foreign body reaction play more significant roles in the bone necrosis around cement.[11,19,24] Saline occupies a greater surface area on the porous surface of the cavity when compared with solid substances like cement or burr. Ideally, for an effective hyperthermia application, bone must be subjected to constant temperature for a certain time that will allow the heat to penetrate the full thickness of bone. This is difficult to control because the transfer of heat from the surface of bone to the center is time related. If the surface temperature is known and kept constant, distribution of heat on bone surface can be estimated using principles of conductive heat transfer and thermal properties of cortical bone tissue. It is impossible to keep a constant temperature with cement or burr. Water is superior to cement and burr because it has full contact with the thin and porous surface of bone and keeps a constant temperature.

The disadvantage of hot water systems is their reliance conductive heat transfer, which is dependent on blood flow rate.[16,18] Regional blood flow is an important variable in determining the efficacy of hyperthermia treatment. Tempereature differences are expected between the two tissues, since tumor tissue has different perfusion compared to normal tissues. Also, microvascular structure of the tumor may be damaged, rendering it prone to hyperthermia induced damage.

In hot saline applications with and without tourniquet, signs of necrosis were observed inside the bone cavity with saline at 80 °C. At this temperature, the surrounding bone, muscle, soft tissues had a normal color, and these subjects did not develop any postoperative complications. None of the applications created heat gradients that would destroy the joint. In conclusion, to extend the borders of curettage in bone cavities, saline should be at 80°C and applied for 12 minutes.

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